For total particulate matter, the consistuent usually considered to be related to the excess of lung cancer risk in smokers. Oogod et al. (1978) concluded that the CET value is "so high that the passive smoker will never inhale more than what equals 1/2 -1 cigarette per day" - a finding consistent with the conclusions of Repace & Lowrey (1980) if adjusted so that a sensible baseline cigarette is used for comparison.

- While more research is certainly needed, there seems at present to be no convincing evidence that passive smoking results in any material risk of serious disease for the healthy nonsmoker.

10. Rylander R.; Peterson Y.; Snella M.-C., ETS - Environmental Tobacco Smoke. Report from a Workshop on Effects and Exposure Levels. March 15-17, 1983, University of Geneva, Switzerland.

- In view of the uncertainty of the ETS exposure in the general population, calculations can not be made regarding the presence of disease such as lung cancer in the non-smoking population due to exposure to ETS by making reference to the data reported in epidemiological studies on the association between smoking and lung cancer.

- An overall evaluation based upon available scientific data leads to the conclusion that an increased risk for non-smokers from ETS exposure has not been established.

11. Fielding J.E.; Phenow K.J.; Health Effects of Involuntary Smoking. New England Journal of Medicine Vol. 319. no.22. December 1, 1988.

- Despite considerable progress in our understanding, of the effects of environmental tobacco smoke, for many conditions the body of studies remains thin. Either too few studies have been undertaken in these instances, or they lack the methodologic rigor necessary to determine a causal link between exposure to tobacco smoke and diseases caused or potentiated by active smoking.

12. Crawford WA, On the Health Effects of Environmental Tobacco Smoke. Occupational and Environmental Health, Sydney, Australia. Arch Environ Health (United States) Jan-Feb '88.

- Possible adverse health effects of breathing environmental tobacco smoke include lung cancer, respiratory illnesses in young children, decreased polmonary function, decreased lung growth, allergy to tobacco, and exacerbation of angina. These effects

2023527276

Source: https://www.industrydocuments.ucsf.edu/docs/xfbl0000

are reviewed to aid informed discussion on this health issue. Some of the constituents of tobacco smoke are found in the home, the outdoor environment, and the workplace in permissible concentrations and are considered unlikely to cause ill health. A double standard, one in the workplace and another for the public, may be evolving for acceptable health risks.

13. Sterling TD; The Author Replies. Journal of Occupational Medicine Volume 29 No. 8 August 1987.

- In fact, Repace and Lowrey did not measure RSP levels in offices under normal conditions of occupancy, smoking, and ventilation. Instead, they estimated average concentrations of 200ug/m in modern offices on the basis of a mathematical model. However, mathematical models are no substitute for measurements under realistic conditions. Repace and Lowrey's model predicts RSP levels that are substanially higher than those observed in offices under normal use.

14. Mantel N., Lung Cancer and Passive Smoking. British Medical Journal. Vol. 294. Feb. 14, 1987.

- Also, the data on cotinine concentrations in the plasma, saliva, and urine reported by Jarvis et al. suggest that the relative risk associated with passive smoking would be quite limited, say of the order 1.05. Passive smokers had, on average, cotinine values 0.5% of the way between the level for those not exposed to passive smoking and the level for active smokers. Assuming active smoking to have a relative risk of 10, added risk of (00%, the predicted relative risk for passive smoking would be 1.045.

  It is interesting that the National Research Council report shows a predicted relative risk 1.14 based on dosimetric considerations. The underlying assumption was that passive smoking had only 1% of the effect of active smoking. That 1% effect was then coupled with a relative risk of 14, added risk of 1400% for active smoking.

  In the event, whether the true relative risk is 1.05 or 1.14, it is unlikely that any epidemiological study has been, or can be, conducted which would permit establishing that the risk of lung cancer has been raised by passive smoking. Whether or not the risk is raised remains to be taken as a matter of faith according to one's choice.

2023527777

Source: https://www.industrydocuments.ucsf.edu/docs/xfbl0000

15. Crawford A.; Passive Smoking. New Zealand Medical Journal, 1987.

- For studies conducted in the United States the relative risk was 1.14 and was not significant as the confidence limits were 0.92-1.40

The Wald 1986 study referred to by Dr. Martin has been vigorously contested by Mantel in the British Medical Journal who has the audacity to suggest that the available data would support a relative risk of 1.05 or 1.14; a risk which would be almost impossible to define. He adds, "Whether or not the risk is raised remains to be taken as a matter of faith according to one" choice.

16. Uberla K, Lung Cancer from Passive Smoking: Hypothesis of Convincing Evidence? Ludwig-Maximilians-Universitat, Munchen, Federal Republic of Germany. Int Arch Occup Environ Health 1987.

- The volume of accumulated data is conflicting and inconclusive. The observations on nonsmokers that have been made so far are compatible with either an increased risk from passive smoking or an absence of risk. Applying the criteria proposed by IARC there is a state of inadequate evidence. The available studies, while showing some evidence of association, do not exclude chance, bias or confounding. They provide, however, a serious hypothesis. Further studies are needed, if one wants to come to an adequate and scientifically sound conclusion concerning the question as to whether passive smoking causes lung cancer in man.

17. Lebowitz MD; The Potential Association of Lung Cancer with Passive Smoking. Division of Repiratory Sciences, University of Arizona College of Medicine, Tuscon, Arizona. Environment International, Vol 12. 1986.

- The biological consequences of smoking require a certain dose over a certain time which if low, may not even be significantly noticed in low doses in large populations (U.S. General, 1982). It seems unlikely that passive smoking is responsible for about one-third of the annual lung cancer mortality among U.S. nonsmokers (Repace and Lowrey, 1985). One must recognize also that nonsmokers may have developed lung cancer from other environmental agents :radon progency may account for 5%-30% (most likely 5%-15%) of such mortality (Edling et al., 1984; Hess et al., 1983; Jacobi, 1984, Radford and St. Clair, 1984), and volatile organic compounds (Albert, 1983; NRC, 1972),

2023527728

Source: https://www.industrydocuments.ucsf.edu/docs/xfbl0000

asbestos (Hirayama, 1981; Holland et al., 1963), and various other environmental factors have been blamed as well. In conclusion, the Repace and Lowrey (1985) estimates of nonsmokers' lung cancer risk from passive smoking is an overstatement.

Lung cancer risk estimated to be twice as high in passive smokers as in nonsmokers not exposed to the smoke of their partner is hardly conceivable because of the absence of cell modifications in the tracheobronchial tract of passive smokers. Thus, the problem of passive smoking may be too small to measure in population studies.

Further research should include other possible carcinogenic agents and confounding factors, such as occupational exposure, other exposures of the nonsmoking household members, social status and other risk variables.

18. Friedman GD; Passive Smoking in Adulthood and Cancer Risk. American Journal of Epidemiology Vol. 128. no., 2 1987.

- It is unfortunate that Sandler et al. did not obtain information on, or account for, additional possible confounding variables in their study. The only ones that they report having included were age, sex, race, active smoking, education, blue collar vs. white collar occupation, and parental smoking. We have found that the amount of passive smoking was correlated with self-reported exposure to occupational hazards, use of marijuana, and alcohol intake. Thus, for example, the increased risk of breast cancer observed by Sandler et al, may be due to increased alcohol intake rather than to passive smoking.

19. Garfinkel L; Joubet L, Involuntary Smoking and Lung Cancer, Some Object Lessons. American Cancer Society, New York

- Elsewhere I have referred to the difficulty of conducting a case-control study where a suspect variable has already been stigmatized and the stigma given wide notoriety. That would seem to explain what has been found by Garfinkel and associates, but even a little thought could have been protective. Their report is always in terms of smoking by husbands and lung cancer in wives, yet the actual association is between smoking by husbands as reported by respondents and the lung cancer of their wives. We know only what the replies to questions were, not what really happened. How were those replies influenced by circumstances, and to what extent were they dependent on who the respondent was?

2023577729

Source: https://www.industrydocuments.ucsf.edu/docs/xfbl0000

20. Heller W-D, Lung Cancer and Passive Smoking. The Lancet. December 3, 1983.

- My calculations suggest that the latest data do not show as clear an association between a woman's lung cancer risk with her husband's smoking habits as the earlier data did. Indeed, relative risks calculated from the additional data re 1,2-0, 1.8, and 1.8 do not show the dose-response relation seen earlier. This doubt, added to doubts about the hislogical evidence and the use of cases and controls from different hospitals (limitations which Trichopoulos et al. concede,) prompts one to ask if the study really does add to the evidence implicating passive smoking as a factor in lung cancer.

21. Pershagen G., Review of Epidemiology in Relation to Passive Smoking. Arch. Toxicol. Suppl. 9, 1986.

- The urinary cotinine excretion proved to be the best indicator of exposure. It is not known, however, how well this indicator correlates with exposure to the agents responsible for the health effects discussed below.

- Exposure to environmental tobacco smoke under experimental conditions does not seem to have a major acute effect on pulmonary function in normal subjects, while the evidence is contradictory in asthmatics. Epidemiological studies on passive smoking and pulmonary function also give somewhat conflicting results. To some extent this probably has to do with differences in methodology, e.g. in the pulmonary function measures used and in the control of confounding factors.

- Systematic errors in the comparison of risks in different exposure groups with regard to passive smoking may have been introduced by an inadequate control of confounding factors. Occupational exposure factors or outdoor air pollution have not been controlled. Other exposures in the homes than tobacco smoke may be of importance, e.g. combustion products from appliances for heating and cooking. The major causes behind the very high lung cancer incidence among Cantonese women are not known and thus could not be controlled in the analysis of passive smoking and lung cancer among women in the studies from Hong Kong (Chan and Fung 1982; Koo et at. 1984).

2023547780

Source: https://www.industrydocuments.ucsf.edu/docs/xfbl0000

22. Crawford W. Allan, Passive Smoking. The Medical Journal of Australia, Vol. 146, February 2, 1987.

- I would also take issue with other statements or omissions in the article, namely; the estimate of passive smoking is given as equivalent to smoking three to five cigarettes per day - this is the top end of the range of estimates from 0.1 to three to five, that is provided by the Commonwealth Department of Health; misclassification of subjects as non-smokers is important and in 11 of 12 studies it is considered possible (NHMRC report); dose response was not evident in five of 10 studies, and not reported in other two studies.

23. Uberla, K., Epidemiology: Its Scope and Limitations for Indoor Air Quality. International Archives of Occupational and Environmental Health, (1987), 59:

- Therefore, relative risks smaller than 2 are generally difficult to reproduce. They are then beyond the threshold of human perception and knowledge.

  Incidences smaller than 10^{-5} to 10^{-6} can usually not be reproduced in cohort studies. They are then beyond the threshold of human perception and knowledge.

- The study was not designed to test this hypothesis, but to screen for a wide variety of possible risk factors. It therefore cannot prove the hypothesis. the cohort was not representative of the population. There was an age selection bias. The indicator by which the exposure was measured-being married to a man who smokes- was neither reliable nor valid, nor specific. Also the end point was not assessed with validity. We know from experience that lung cancer diagnosis on the death certificate might be erroneous. Confounding factors were not adequately considered, for instance working place, air pollution or medical care. Bias in registering the fact that a woman was a non-smoker was neither controlled nor excluded. Differential misclassification is likely, since in 1965 smoking women were very rare in Japan. Almost nothing is known of the 200 cases. Case reports are missing; autopsy and histology are available in 11.5%.

2023577781

Source: https://www.industrydocuments.ucsf.edu/docs/xfbl0000

- Another large prospective study from GARFINKEL in the US could not show a risk increase. I carefully evaluated the available studies last year and published the evidence with a critical view. I cannot describe the 10 case-control studies here in detail. They all have much weaker evidence compared to the HIRAYAMA study.

- Whether passive smoking causes lung cancer is an open question today. It is therefore not scientifically sound to calculate the attributable risk, i.e. the possible number of deaths attributed to passive smoking per year. All serious scientist refrain from such calculations. Of course, it cannot be excluded that there is a causal relationship. If there is an effect, it is likely to be very compared to other risks.

  The majority of criteria for a causal connection are not fulfilled. There is no consistency, there is a weak association, there is no specificity, the dose-effect relation can be viewed controversially, bias and confounding are not adequately excluded, there is no intervention study, significance is only present under special conditions and the logical plausibility can be judged controversially.

- What can we learn from such a case study in low risk association? Toxicological studies alone cannot provide evidence on the size of a risk to man from indoor air pollution. There is not a single animal study with ETS which succeeded in producing lung cancer. Epidemiologic studies are the way to ascertain whether there is a risk in man, and what the size of the risk is. There are thresholds for human perception and knowledge in epidemiology: relative risks smaller than 2 and incidences smaller than 10^{-5} to 10^{-6} are such thresholds. The concept of a missing threshold for carcinogens should be replaced by more sophisticated models, when one tries to assess the cancer risk of indoor air quality.

24. Brown R.C., Environmental Tobacco Smoke in the Context of Indoor Air Quality. Human Toxicol, 1989.

- Lung cancer and respiratory disease in children are the health risks most researched, while possible effects of ETS on the incidence of cardiovascular disease and on the prognosis of persons who already suffer from cardiovascular disease run a poor third. Interestingly there is little persuasive evidence that exposure to ETS leads to decreased lung function in exposed adults.

2023577782

Source: https://www.industrydocuments.ucsf.edu/docs/xfbl0000

- A majority, but not all, of the published reports have shown a higher lung cancer risk in the non-smoking women married to smokers. However many of the studies are small and open to a variety of methodological criticisms, and few have come up with differences in risk that are statistically significant. On the assumption that it is legitimate to combine the results of different studies several investigators have pooled the data from multiple studies and subjected them to, so-called, 'meta-analysis'.

  These authors by pooling ten case-control and three prospective studies calculated a relative risk for lung cancer of 1.35 (confidence limits 1.19-1.54), this figure has been widely assumed to be meaningful.

- However, not everyone accepts the meta-analysis is a legitimate procedure or that the calculations made by Wald et al. are appropriate. Thus, Letzel et al. examined all 1023 combinations of the ten case-control studies and found that only 24 of these combinations gave a risk significantly greater than unity. furthermore the significance in these 24 combinations was largely determined by only three studies which they considered to be particularly flawed.

25. Burch, P.R., Letter to the Editor, Re: Passive Smoking in Adulthood and Cancer Risk. (Letter to the Editor). Am. J. or Epidemiology, 1986.

- The assumption by Sandler et al. that the smoking status of the spouse is a useful measure of exposure to ambient cigarette smoke is, therefore, highly suspect. This doubt is borne out by their own study of lung cancer cases in which "... there was no apparent dose-response using either years married to a smoker or average amount smoked by spouse as the measure of dose..." The observed cancer associations were with the status of the spouse and not with exposure to cigarette.

26. Crawford, A., Hazards in the Air We Breathe.

- In the neighbouring Republic of China, joint studies by the Chinese and Americans (Mumford et al) have found extremely high rates of lung cancer in nonsmoking women which is ascribed to the fuels used in cooking and the indoor pollution which results. The highest rate of lung cancer was 287 per 100,000. In another joint study Gao et al. in Shanghai, the Chinese authorities and the US NCI also reported high

2023577783

Source: https://www.industrydocuments.ucsf.edu/docs/xfbl0000

rates, partly ascribable to the PAHs from cooking oils, particularly rapeseed oil. There may well be some relevance in these studies to the findings by Hirayama of the highest RRs in the wives of agricultural workers in Japan.

- In France, Benhamou et al, 1988, have confirmed some of the Doll and Peto observations on lung cancer risks in certain occupations. RRs for farmers 1.24(0.94 - 3.37), miners and quarrymen 2.14 (1.07-4.3), plumbers and pipe fitters 1.8 (0.96-1.12), and motor vehicle drivers 1.42 (1.07-1.89) after controlling for smoking were recorded.

- "The general view is that exposure to carcinogens does not have a threshold below which there is no effect", is expressed as one criterion by Wald et al. in concluding that ETS causes lung cancer. If this is accepted for ETS, it should also apply to air pollution in cities. Doll and Peto note that it is difficult to make due allowance for the difference in effect of some 20 years of exposure in industrial premises and 70 years of lower levels of pollution in general. It is to be noted that the exposure starts at birth when sensitivity is greatest and defense mechanisms in humans are immature. Doll and Peto also express the view that when confounding factors are taken into account it may not be possible to distinguish between little or no effect of ambient air carcinogenic pollutants. A doubling of the lung cancer rates in cities compared to rural areas has been reported, a 100% increased risk.

- They express the view that "the questionable results from studies with a poor design will not lead to a valid meta-analysis with scientifically convincing results." Like Lee, they express concern about the major problem of misclassification.

- One may recall or certainly be aware of the Epilogue by Ernst L. Wynder to the Guidelines to the Epidemiology of Weak Associations in 1985 organized by the American Health Foundation:

  "But, when it comes to lesser associations, errors in epidemiological techniques can falsely show a positive association when in fact no association exists or find no association, even if one does exist."...

  "When the design of the study is scientifically accurate, if the cases and the controls are properly selected, if possible biases and confounders have been properly considered and avoided, if the problem of subgroup analysis is clearly understood, and if the

2023577784

Source: https://www.industrydocuments.ucsf.edu/docs/xfbl0000

entire evidence is subjected to a careful review of the criteria, it is likely that the proper judgment will have been made. At times, however, such care is not given to epidemiological studies and their interpretations. We are concerned that in the "rush to publish", often as a preliminary report, false associations are reported which do justice neither to the factor being incriminated as harmful, nor to public safety when indeed a risk does not exist, nor to the science of epidemiology".

- Pearce from the US and Howard from New Zealand in their study of occupation, social class and male cancer mortality had a cut off of RR 1.5 in their occupational groups because relative risks less than 1.5 are particularly likely to be due to bias or confounding. A problem discussed by Doll (1985) in relation to occupational disease is that of how to interpret RRs of 1.2-2.0 when confounding by general socioeconomic, cultural or geographic factors occurs as is certainly noted in part in the ETS debate when East and West results are considered. Geoffrey Rose (1987) from UK also advises the RRs of 1.5 or less will almost certainly be undetectable in his paper related to environmental factors.

1. The nonsmokers are exposed to one chemical peculiar to cigarette smoke - nicotine - and this is measured as the metabolite cotinine.

2. There are confounders in the workplace for the induction of lung cancer.

3. There are confounders for lung cancer via air pollution in industrialized countries.

4. There is no convincing evidence of an increase of lung cancer in nonsmokers during the decades of increasing prevalence of smoking.

5. There are inadequate data on the epidemiology of ETS in the work place.

- If possible these scientists should be "blinded" as to the nature of the substance to be assessed for risk and thus avoid personal biases.

The advice which I would give on the subject of exposure to environmental tobacco smoke to a Minister or Secretary of State for Health which he should convey to his decision making colleagues who collectively are responsible to the public would include.

2023577785

Source: https://www.industrydocuments.ucsf.edu/docs/xfbl0000

1. The increased relative risks for lung cancer in nonsmokers so far reported in epidemiological studies are contentious and small and relate to a rare disease. Inmost studies the findings are not statistically significant.

2. There has been no change in lung cancer rates in nonsmokers over many decades despite changes in cigarette consumption. This change should have occurred if exposure to ETS induces lung cancer as is claimed by some.

3. All the studies have been confounded by failure to take into account the toxic substances inevitably present in the air inside homes.

4. Carcingoenic substances are released by the combustion of all fossil fuels and are ubiquitous. They have been detected and measured in city streets, offices, factories and homes.

5. Carcinogenic substances are released when many foodstuffs are braised, broiled, grilled or barbecued.

6. Carcinogens are released abundantly in the exhausts of motor cars and trucks which use petrol or diesel fuels, the latter being of greater importance qualitatively.

7. Carcinogens are present in many workplaces and some are released into the local air environment.

8. Many of the hypothetical risks of lung cancer are based on the questionable assumption that for carcinogens there is no threshold for exposure, i.e., there is no a "No Effect" level (NEL).

9. ETS is but one of may sources of carcinogens, each of which is present in immeasurable small numbers.

10. The fear of ETS exposure is being engendered as a tactic in the general strategy of achieving active smoking cessation.

11. The visible presence of ETS dispersed in offices, workplaces and homes is evidence that the ventilation is inadequate and is a warning sign that other non-visible air pollutants will also be inadequately controlled.

12. Adequate ventilation of areas and reasoned tolerance of individual attitudes to smokers are the keys to solving the current concerns about exposure to environmental tobacco smoke.

2023527786

Source: https://www.industrydocuments.ucsf.edu/docs/xfbl0000

- There are not, at the present time, the needed reliable reproducible measurements of exposures to environmental tobacco smoke nor reliable reproducible epidemiological data to warrant the regulatory actions which have been taken by some authorities and purported to be of benefit to the health of the public.

  If regulators are to intervene to remove one complex of low concentrations of chemicals from indoor air because it presents a hypothetical hazard to health, then on the same hypothetical grounds the incomplete combustion of all vegetable matter and fossil fuels should also be subject to intervention by regulators.

2023577787

Source: https://www.industrydocuments.ucsf.edu/docs/xfbl0000